REMARKS

Applicant wishes to further address the enablement rejection set forth in the Office Action dated June 16, 2004.

Specifically, the Office alleged on pgs. 10-12 of the Action that:
(1) the specification failed to provide an enabling disclosure for transgenic mice which include unrearranged human TCR alpha or beta loci;
(2) that the specification provides no actual data for any mouse made according to the disclosed methods; and
(3) that the expression of functional TCR from unrearranged genomic DNA adds "an extra level of complexity to the equation" and thus increases the unpredictability of achieving successful functional TCR expression.

As to point (2), shown above, Applicants respectfully remind the Office that there is no statutory requirement for "actual data" to obtain a U.S. patent. What is required, for example, by statute is that the specification show how to make and use the invention to one of skill in the field. 35 USC §112, first paragraph. For reasons set out in the prior response and as follows, Applicants have fully satisfied the "how to make" and "how to use" requirements of 35 USC §112.

In further support of Applicants' position, the undersigned requests consideration of the attached Rule 132 Declaration of co-inventor Heather Belmont ("Declaration"). The Declaration establishes, among other things, that one of skill reading the subject application would be able to make and use a transgenic mouse that includes functional human TCR alpha and beta chains, particularly those that are *unrearranged* and are under the control of suitable human regulatory sequences.

Turning now to the Declaration, Heather Belmont ("Belmont") states that is a co-inventor who

personally performed, directed and/or assisted in research that led to the invention. **Appendix B** of the Declaration establishes her knowledge and expertise in the field. Moreover, Belmont states that she has read the outstanding Office Action but respectfully disagrees that is does not enable the invention as claimed. Decl. at ¶¶ 2-4.

The Declaration further states, among other things, that co-inventor Belmont is familiar with unpublished research that was performed by her and her co-inventors or under their direction. According to Belmont, the work shows, among other things, that a worker can produce transgenic mice that include unrearranged human TCRα loci that include multiple V, J, and C gene segments. Such loci can be placed under the control of human regulatory elements and still work in mice. Decl. at ¶¶ 5-6.

As stated by co-inventor Heather Belmont, the unpublished research showing how to make and use such transgenic mice is in line with detailed disclosure and prophetic teachings provided by the subject application. Decl. at ¶¶ 7-9.

In particular, Belmont stated in her Declaration that she and her co-inventors made human TCRα and TCRβ transgenes using publicly available information and other information provided by the subject application. Decl. at ¶ 10.

As stated at ¶11 of the Declaration, Belmont and her co-inventors injected or had injected under their supervision, YAC vectors that included the TCRα and TCRβ transgenes. As also stated, for instance, they successfully produced transgenic mice that were tested for vector integration. One heterozygous founder mouse had complete integration of the human TCRβ YAC spanning the entire transgene. Decl. at ¶ 11. Another heterozygous founder injected with the human TCRα YAC vector demonstrated integration that spanned 10 TRAV segments, 61 TRAJ segments, and the TRAC gene segment of the human TCRα gene. Decl. at ¶ 11

The information provided by the Declaration, particularly at ¶ 11 shows, among other things, that in line with the guidance provided by the specification, it is certainly possible to integrate the human TCRα and TCRβ genes into mice. It also shows, among other things, that one can produce heterozygous mice that can serve as founders for homozygous progeny.

According to the Declaration at ¶12, Heather Belmont determined that the transgenic mice she produced with her co-inventors made transcript that encoded human TCRα. The procedures she used were in line with the disclosure provided by the subject application. Decl. at ¶12.

More specifically, the data provided by the Declaration at ¶12 and **Appendix A** shows, among other things, that human TCRα transcripts were present only in mice that had an integrated human TCRα transgene. As Heather Belmont states, the data is consistent with occurrence multiple rearrangement events during production of the transgenic mice. The data is further consistent with sufficient thymocyte maturation, including positive and negative selection, within the founder mice. Decl. at ¶12.

The data shown in **Appendix A** are explained in detail in ¶13 of the Declaration by co-inventor Belmont.

As stated by Belmont at ¶14 of the Declaration, one reading the subject application would appreciate that it provides sufficient disclosure to make and use the claimed transgenic mice. See also ¶13 of the Declaration and **Appendix A**.

In view thereof, it is respectfully submitted that concerns raised at pgs. 10-12 of the Action, for instance, have been addressed. Applicants have made appropriate founder transgenic mice that include unrearranged human T-cell receptor alpha and beta transgenes. Molecular data showing

successful transcription of human TCRα genes in the mice has been provided.

Applicants believe that additional fees are not required in connection with the consideration of the within matter. However, if for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105.**

Respectfully submitted,

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